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Research paper

Mortality impact of empirical antimicrobial therapy in ESBL- and AmpC-producing Enterobacteriaceae bacteremia in an Australian tertiary hospital

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Abstract *Background:* Treatment of ESBL- and AmpC-producing Enterobacteriaceae bacteremia is often complicated by lack of appropriate antibiotics. We aimed to determine the predictors of mortality and impact of empirical antibiotics.
Methods: A retrospective observational study was performed on consecutive adult cases of ESBL and AmpC bacteremia at the Alfred Hospital from 2014 through April 2018.
Results: Among 110 patients with ESBL (88.2%) and AmpC (14.5%) bacteremia episodes, 96.4% had comorbidities such as hematological malignancy (30%). Approximately 45% were on immunosuppressive drugs, while 69% had recent antibiotic exposure. Over 84% of bacteremias were hospital acquired or healthcare associated. Urinary tract was the main source of infection (40%) with *E. coli* being the commonest organism (66.4%). The isolates were least resistant to gentamicin (21.8%), which was often appropriately used in empirical therapy. About 34% of patients presented with severe sepsis or shock. The 30-day mortality rate was 20% with no correlation with inappropriate empirical antibiotics (52%). There was no significant mortality difference between carbapenem use in empirical and definitive therapy. Respiratory source [OR 11.77, 95% CI 1.30–106.85; $p = 0.03$], severe sepsis or shock [OR 5.17, 95% CI 1.37–19.55; $p = 0.02$] and inappropriate definitive therapy [OR 27.93, 95%CI 3.69–211.35; $p = 0.001$] were independent predictors for mortality.
Conclusion: The choice and appropriateness of empirical therapy were not associated with mortality in ESBL and AmpC bacteremia. Prudent use of carbapenem is reasonable with gentamicin as alternative. Emphasis should be on prompt resuscitation in severe sepsis and early detection of ESBL and AmpC to facilitate appropriate switch to definitive therapy.

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Highlights

- The 30-day mortality rate of ESBL and AmpC bacteremia was 20%.
- Inappropriate empirical antibiotic therapy was not associated with increased mortality.
- There was no significant mortality difference between carbapenem use in empirical and definitive therapy.
- Gentamicin was often appropriately used in empirical therapy.
- Emphasis should be on prompt resuscitation in severe sepsis and early detection of ESBL and AmpC.

Introduction

Enterobacteriaceae such as *Escherichia coli* (*E. coli*) and Klebsiella species are increasingly resistant to antibiotics [1,2]. This phenomenon is largely driven by the production of extended spectrum beta-lactamases (ESBL) and to a lesser extent, AmpC beta-lactamases. The global incidence of infection with ESBL-producing Enterobacteriaceae (ESBL-E) has been rising in recent years, although at present it remains relatively low in Australia compared to some Asian countries and parts of Europe [3]. In Australia, ESBL phenotype was found in 7—12% of *E. coli* and 4—7% of *Klebsiella pneumoniae* [4]. Resistance due to plasmid-mediated AmpC enzymes is less common than ESBL in most parts of the world but may be both harder to detect and broader in spectrum [5].

At the Alfred Hospital, there are more than 300 ESBL- and AmpC-producing Enterobacteriaceae (AmpC-E) isolated with over 20 cases of confirmed bloodstream infections (BSI) each year. The extensive antimicrobial resistance conferred by ESBL and AmpC enzymes may result in therapeutic dilemma among our clinicians, especially in the setting of initiating empirical therapy for patients who presented with sepsis. As carbapenem is accepted as the most reliable antibiotics against ESBL and AmpC infections [6], increasing prevalence of these isolates often drives empirical usage of carbapenem, which in turn could result in the emergence of carbapenem-resistant Enterobacteriaceae (CRE) [7—9] and *Acinetobacter baumannii* [10].

Carbapenem sparing antibiotics have been suggested in the treatment of ESBL-E and AmpC-E infections. Some studies propose that piperacillin—tazobactam may be a reliable option for the treatment of BSI due to ESBL-producing Gram-negative bacilli [11—15]. Nonetheless, the recent MERINO trial failed to demonstrate non-inferior 30-day mortality of definitive treatment with piperacillin—tazobactam compared with meropenem for ESBL *E. coli* and *K. pneumoniae* BSI (12.3% versus 3.7%) [16]. As for AmpC-producing organisms, cefepime may be a reasonable option for the treatment of invasive infections particularly when adequate source control is achieved [17]. In contrast to definitive therapy, there is a dearth of evidence on the impact of empirical therapy, particularly with non-carbapenem agents on the outcome of ESBL-E and AmpC-E sepsis.

This study sought to assess the clinical characteristics of ESBL-E and AmpC-E bacteremia in Alfred Hospital and to determine the predictors of 30-day mortality with particular focus on empirical antibiotics. Our secondary objective was to evaluate the appropriateness of antibiotics used in empirical therapy.

Methods

Study population and data collection

The Alfred Hospital is a major public hospital in Melbourne, Victoria. Equipped with over 600 beds, The Alfred has one of Australia's busiest emergency and trauma centres, the state's largest intensive care unit and Victoria's only heart and lung transplant service.

We conducted a retrospective study at the Alfred Hospital to analyse consecutive cases of ESBL-E or AmpC-E bacteremia from January 2014 through April 2018. Cases were identified from the microbiology laboratory database, followed by review of electronic patient medical records stored in Cerner's Power Chart program. Demographic information and clinical data including age, gender, comorbidity, previous antibiotic exposure, use of immunosuppressive therapy, source of infections, severity of sepsis at presentation, antibiotics given and mortality outcome were extracted using standardized data collection sheets. Secondary outcomes including relapse or persistent bacteremia and acquisition of fungal or other multi-resistant bacterial sepsis were also reviewed.

Definitions

Bacteremia onset was the day on which the first ESBL or AmpC positive blood culture was drawn. Bacteremia was considered hospital acquired if the blood culture sample was taken 48 h after hospital admission. Episodes were considered health care associated according to the criteria of Friedman et al. [18]. The source of bacteremia was determined by clinician's assessment and appropriate cultures from relevant sites if available. Recurrent urinary tract infections (UTIs) implied at least 3 UTIs requiring antibiotic treatment in the year prior to bacteremia onset. Neutropenia was defined as an absolute neutrophil count of $<$500 cells/mm3 at the onset of the bacteremia. Comorbidities were assessed by using the Charlson comorbidity score [19]. Severe sepsis and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [20]. Mortality was defined as inpatient death due to any cause within 30 days of bacteremia onset. Bacteremia

was considered relapsed or persistent if the same ESBL-E or AmpC-E was isolated from the blood culture repeated after 48 h.

Empirical therapy consisted of antibiotics given in the first 24 h of bacteremia onset. Definitive therapy was defined as antibiotics instituted after blood culture results were known. Appropriateness of non-beta-lactam antibiotics including ciprofloxacin and gentamicin was based on in vitro susceptibility of the organism isolated. Apart from carbapenem, all beta-lactam antibiotics were considered inappropriate regardless of in vitro susceptibility. There were 2 exceptions to the rule. We considered piperacillin—tazobactam and cefepime to be appropriate antibiotics in ESBL-E and AmpC-E bacteremia respectively, if the organisms showed in vitro susceptibility. The minimal inhibitory concentration (MIC) clinical breakpoints were $\leq$8 mg/L for piperacillin—tazobactam and $\leq$1 mg/L for cefepime, according to the 2018 European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria [21]. Intermediate susceptibility was classified as non-susceptible in this study. Combination therapy was considered to be appropriate if comprised at least one appropriate antibiotics. The dosage, frequency and route of antibiotics were not taken into consideration when assessing appropriateness. All study definitions were established before data analysis.

Microbiological studies

Antimicrobial susceptibility testing and phenotypic confirmation of ESBL-E and AmpC-E were performed according Clinical Laboratory Standards Institute (CLSI) recommendations. Vitek 2 system (bioMérieux SA, Marcy l'Etoile, France) MIC profile was used as a screening test. Screen-positive isolates (MIC of cefotaxime or ceftazidime of $\geq$1 mg/L, an ESBL or inducible cephalosporinase warning by the automated system) were subjected to confirmation tests using double disc synergy method and boronic acid disk test for ESBL and AmpC respectively.

Statistical analysis

Baseline characteristics were compared using Chi-square or Fisher's exact tests where applicable for categorical variables and independent t-test for continuous variables. Variables with p-value of $<$0.10 from univariate analysis were included in a multivariable logistic regression analysis for predictors of 30-day mortality. Predictors with p-value $<$0.05 were considered significant and retained in the final multivariate model. IBM SPSS Statistics software version 22 was used for all statistical analyses.

Results

Patient characteristics

There were 114 episodes of ESBL or AmpC bacteremia, 4 (3.5%) of which were excluded in the study due to insufficient inpatient record. Out of the remaining 110 episodes, 58.2% of the patients involved were males. The mean age was 64.8 years ($\pm$17.1). Over 96% of them had comorbidities such as haematological malignancy (30.0%), heart failure (28.2%), diabetes mellitus (24.5%) and obstructive urinary tract disease (24.5%). About 45% had been given immunosuppressive drugs in the past 3 months and at least 22% were neutropenic at the onset of bacteremia. Only 11.8% of patients were admitted to intensive care unit in the last 3 months and 20% were known to have ESBL or AmpC colonization or infection. Majority of the patients (69.1%) had been exposed to antibiotics 3 months prior to the onset of bacteremia. Piperacillin—tazobactam (16.4%), ciprofloxacin (15.5%), and trimethoprim (15.5%) were the commonest antibiotic exposure documented. Only 8.2% of patients were exposed to ceftriaxone (Table 1).

Characteristic of ESBL and AmpC bacteremia

Most of the infections were classified as healthcare associated (47.3%) or hospital acquired (36.4%), while only 15.5% were community acquired. Urinary tract was the presumed source of bacteremia in 44 patients (40.0%). The organisms isolated from blood samples mainly consisted of *E. coli* (66.4%) and Klebsiella sp. (30.0%). At least 34% of patients presented with severe sepsis or septic shock within 24 h of onset of bacteremia (Table 1).

Antimicrobial resistance

As illustrated in Fig. 1, majority of isolates were ESBL producers (88.2%). Only 14.5% had AmpC related resistance. In the analysis of other antimicrobial co-resistance, ciprofloxacin was found to have the highest resistance rate (72.7%), followed by cefepime (68.2%). Gentamicin and piperacillin—tazobactam had lower resistance rate, namely 21.8% and 40.0% respectively. All the isolates were susceptible to carbapenem.

Antibiotic therapy

Just over half (51.8%) of the empirical antibiotics given were considered to be inappropriate. Our patients predominantly received non-carbapenem agents (83.6%) as initial empirical therapy. Piperacillin—tazobactam was most frequently prescribed (30.9%), followed by ceftriaxone (20.9%). Gentamicin was often appropriately used in combination therapy. For instance, gentamicin was twice likely to be appropriate therapy [RR 2.27, 95% CI 1.82—2.82; $p < 0.01$] when given together with ampicillin or ceftriaxone, both of which were invariably inappropriate as monotherapy in the setting of ESBL-E and AmpC-E bacteremia (Table 2). As for definitive therapy, carbapenem was largely preferred (78.7%) once ESBL-E or AmpC-E results were known. Nine patients (8.3%) failed to receive appropriate definitive therapy. Two patients were excluded from analysis of definitive therapy as they died within 24 h of presentation before culture results were available (Table 3).

Mortality

The all-cause mortality rate within 30 days after the onset of ESBL-E and AmpC-E bacteremia was 20%. The findings of

Table 1 Baseline characteristics of patients with ESBL-E and AmpC-E bacteremia.

Characteristics	n = 110 (%)
Men	64 (58.2)
Mean age (SD)	64.8 (±17.1)
Comorbidity	106 (96.4)
Hematological malignancy	33 (30.0)
Heart failure	31 (28.2)
Diabetes mellitus	27 (24.5)
Obstructive urinary tract disease[a]	27 (24.5)
Chronic renal failure	20 (18.2)
Chronic pulmonary disease	16 (14.5)
Solid tumour	16 (14.5)
Liver cirrhosis	11 (10.0)
Hemopoietic stem cell transplantation	11 (10.0)
Solid organ transplantation	11 (10.0)
Hemiplegia or paraplegia	6 (5.5)
Charlson comorbidity index > 3	73 (66.4)
Immunosuppressive treatment[b]	49 (44.5)
Neutropenia	24 (21.8)
Indwelling urinary catheter dependent	7 (6.4)
History of recurrent urinary tract infections	15 (13.6)
Known ESBL/AmpC colonization or infection	22 (20.0)
Overseas travel in the past 6 months[c]	3 (2.7)
ICU admission within last 90 days	13 (11.8)
Antibiotic exposure in the past 90 days	76 (69.1)
Piperacillin—tazobactam	18 (16.4)
Fluoroquinolones	17 (15.5)
Trimethoprim	17 (15.5)
Ceftriaxone	9 (8.2)
Carbapenem	8 (7.3)
Cefepime	3 (2.7)
Place of acquisition	
Community acquired	17 (15.5)
Healthcare associated	52 (47.3)
Hospital acquired	40 (36.4)
Source of bacteremia	
Urinary tract	44 (40.0)
Intra-abdomen[d]	25 (22.7)
Respiratory	6 (5.5)
Central vascular catheter	4 (3.6)
Others	6 (5.5)
Unknown	24 (21.8)
Presentation with severe sepsis or septic shock	38 (34.5)

[a] Including neurogenic bladder.
[b] Including chemotherapy and steroids.
[c] 3 patients had travelled to Indonesia, India and Cambodia respectively. One of the patients was hospitalized in Bali, Indonesia.
[d] Including biliary tract infections.

univariate analysis of risk factors associated with mortality are reflected in Table 3. None of the patients with community acquired sepsis died. Bacteremia originated from urinary tract had the lowest mortality rate (6.8%) compared to those from other sources. The mortality rate was comparable between those who received empirical carbapenem (27.8%) and non-carbapenem (18.5%) antibiotics [p = 0.35]. As opposed to definitive therapy, inappropriate empirical antibiotics were not significantly associated with mortality. In multivariate analysis, respiratory source [odds ratio (OR) 11.77, 95% confidence interval (CI) 1.30—106.85; p = 0.03], severe sepsis or shock [OR 5.17, 95% CI 1.37—19.55; p = 0.02] and inappropriate definitive antibiotic therapy [OR 27.93, 95% CI 3.69—211.35; p = 0.001] were independent predictors of 30-day mortality (Table 5). Furthermore, a sub-analysis selecting patients with severe sepsis or septic shock did not demonstrate significant association between empirical therapy and mortality (Table 4).

Secondary outcomes

Among 97 patients (88.2%) who had blood cultures repeated after 48 h of bacteremia onset, only 3 (3.1%) had persistent or relapse ESBL-E bacteremia within 30 days. All 3 of them had received inappropriate and non-carbapenem antibiotics as empirical therapy. Additionally, 1 patient developed candidemia, while 2 patients acquired *Stenotrophomonas maltophilia* and *Enterococcus faecium* bacteremia respectively within 30 days of ESBL-E onset. They were given carbapenem definitive therapy, although 2 of them had initially received non-carbapenem empirical therapy. There was no significant correlation between antibiotics received and these secondary outcomes.

Discussion

Although there is rising community-acquired ESBL infections and concomitant high rates of fecal colonization by ESBL-producing bacteria worldwide [22—24], 84.5% of our ESBL-E and AmpC-E bacteremia episodes were either hospital acquired or healthcare associated. Our results concurred with a Dutch cohort in which 84% of ESBL BSI were nosocomial or otherwise healthcare associated [25]. This suggests that in developed countries, healthcare exposure remains a predominant risk factor for ESBL and AmpC infections. Our study cohort comprised of older population with various comorbidities such as hematological malignancy, diabetes mellitus, heart failure and obstructive uropathy, which predisposed them to frequent hospitalizations, home therapy or long-term care facility.

Multiple studies have demonstrated an association between previous antimicrobial exposure and acquisition of ESBL-E and AmpC-E infections [26—31]. Third generation cephalosporins have been recognized as the main driver of these resistant organisms [32,33]. Interestingly, only a small proportion of our patients were given ceftriaxone prior to bacteremia onset. Many of our patients were instead exposed to ciprofloxacin, trimethoprim/±sulfamethoxazole and piperacillin—tazobactam, which were commonly prescribed to our haematological and transplant patients either as prophylaxis or treatment. Trimethoprim was also one of the first line oral antibiotics for urinary tract infections.

Another observation that merit mention is that 20% of our cohort was known to have ESBL-E or AmpC-E colonization or infection. Various studies have supported persistent faecal colonization with ESBL-producing bacteria [34,35]. In a meta-analysis, 19% of patients with solid or haematological malignancy were colonised with ESBL-E and the risk

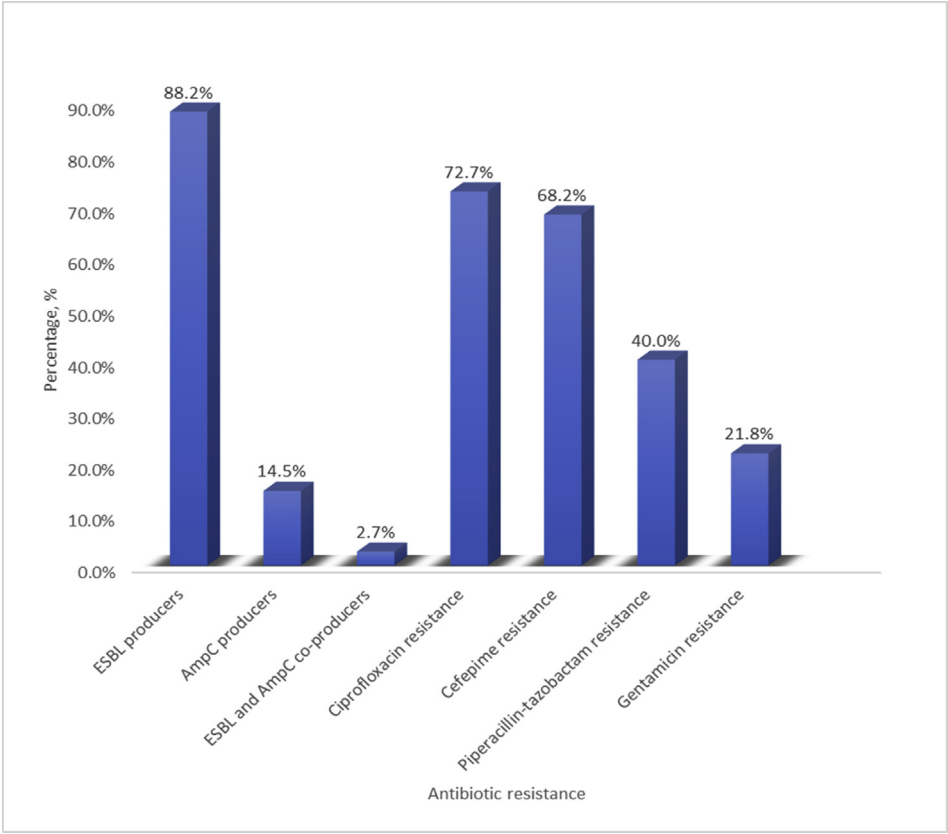

Figure 1 Proportion of different antibiotic resistance detected in ESBL-E and AmpC-E isolates.

Table 2 Empirical antibiotics according to appropriateness of therapy.

Antibiotics[a]	Total n = 110 (%)	Appropriate n = 53 (48.2%)	Inappropriate n = 57 (51.8%)	p value	RR (95% CI)
Monotherapy					
Meropenem	15 (13.6)	15 (28.3)	0	<0.001	2.50 (1.95–3.20)
Piperacillin–tazobactam	34 (30.9)	17 (32.1)	17 (29.8)	0.80	1.06 (0.70–1.59)
Cefepime	4 (3.6)	0	4 (7.0)	0.12	–
Gentamicin	4 (3.6)	2 (3.8)	2 (3.5)	1.00	1.04 (0.38–2.82)
Ciprofloxacin	3 (2.7)	0	3 (5.3)	0.24	–
Ceftriaxone	23 (20.9)	0	23 (40.4)	<0.001	–
Amoxicillin–sulbactam	1 (0.9)	0	1 (1.8)	1.00	–
Cephalexin	1 (0.9)	0	1 (1.8)	1.00	–
Combination therapy					
Gentamicin + ampicillin or ceftriaxone[b]	8 (7.3)	8 (15.1)	0	<0.01	2.27 (1.82–2.82)
Gentamicin + cefepime	2 (1.8)	2 (3.8)	0	0.23	2.12 (1.74–2.59)
Gentamicin + piperacillin–tazobactam	2 (1.8)	1 (1.9)	1 (1.8)	1.00	1.04 (0.26–4.21)
Ceftriaxone + ciprofloxacin	2 (1.8)	2 (3.8)	0	0.23	2.12 (1.74–2.59)
Piperacillin–tazobactam + ciprofloxacin	3 (2.7)	3 (5.7)	0	0.11	2.14 (1.75–2.62)
Meropenem + gentamicin	2 (1.8)	2 (3.8)	0	0.23	2.12 (1.74–2.56)
Meropenem + gentamicin + ciprofloxacin	1 (0.9)	1 (1.9)	0	0.48	2.10 (1.72–2.55)
Other antibiotic regimen[c]	3 (2.7)	0	3 (5.3)	0.24	–
No antibiotics	2 (1.8)	0	2 (3.5)	0.50	–

[a] Vancomycin, daptomycin, doxycycline and azithromycin were excluded.
[b] Gentamicin combination therapy with either ampicillin or ceftriaxone, both of which were invariably inappropriate as monotherapy.
[c] 3 patients received empirical monotherapy with benzylpenicillin, flucloxacillin and clindamycin respectively.

for subsequent BSI was increased by almost 13 times [36]. A case control study showed that urinary catheterization [OR 5.2, 95% CI 1.984–13.569; p = 0.0008] and use of beta-lactam/beta-lactamase inhibitor prior to infection [OR 3.2, 95% CI 1.073–9.864; p = 0.037] were risk factors for ESBL *E. coli* infection in colonized patients [37].

Table 3 Factors associated with 30-day mortality among patients with ESBL-E or AmpC-E bacteremia.

Variables	All patients n = 110 (%)	Death n = 22 (20.0%)	Survival n = 88 (80.0%)	p value
Men	64 (58.2)	15 (68.2)	49 (55.7)	0.29
Mean age (SD)	64.8 (±17.1)	59.5 (±17.5)	66.1 (16.9)	0.10
Comorbidity				
Hematological malignancy	33 (30.0)	11 (50.0)	22 (25.0)	0.02
Heart failure	31 (28.2)	6 (27.3)	25 (28.4)	0.92
Diabetes mellitus	27 (24.5)	4 (18.2)	23 (26.1)	0.44
Obstructive urinary tract disease	27 (24.5)	4 (18.2)	23 (26.1)	0.44
Chronic renal failure	20 (18.2)	5 (22.7)	15 (17.0)	0.54
Chronic pulmonary disease	16 (14.5)	1 (4.5)	15 (17.0)	0.19
Solid tumour	16 (14.5)	1 (4.5)	15 (17.0)	0.19
Liver cirrhosis	11 (10.0)	1 (4.5)	10 (11.4)	0.69
Hemopoietic stem cell transplantation	11 (10.0)	4 (18.2)	7 (8.0)	0.23
Solid organ transplantation	11 (10.0)	1 (4.5)	10 (11.4)	0.69
Urinary catheter dependent	7 (6.4)	2 (9.1)	5 (5.7)	0.63
Hemiplegia or paraplegia	6 (5.5)	2 (9.1)	4 (4.5)	0.35
HIV	2 (1.8)	0	2 (2.3)	1.00
Charlson comorbidity index > 3	73 (66.4)	13 (59.1)	60 (68.2)	0.42
Immunosuppressive treatment	49 (44.5)	14 (63.6)	35 (39.8)	0.04
Neutropenia	24 (21.8)	10 (45.5)	14 (15.9)	<0.01
Place of acquisition				
Community acquired	17 (15.5)	0	17 (19.3)	0.02
Healthcare associated	52 (47.3)	10 (45.5)	42 (47.7)	0.85
Hospital acquired	40 (36.4)	12 (54.5)	28 (31.8)	0.05
Source of bacteremia				
Urinary tract	44 (40.0)	3 (13.6)	41 (46.6)	<0.01
Intra-abdomen	25 (22.7)	5 (22.7)	20 (22.7)	1.00
Respiratory tract	7 (6.4)	4 (18.2)	3 (3.4)	0.03
Central venous catheter	4 (3.6)	1 (4.5)	3 (3.4)	1.00
Others	5 (4.5)	0	5 (5.7)	0.58
Unknown	26 (23.6)	9 (40.9)	17 (19.3)	0.03
Organisms				
E. coli	73 (66.4)	13 (59.1)	60 (68.2)	0.42
Klebsiella sp.	33 (30.0)	8 (36.4)	25 (28.4)	0.47
Enterobacter sp.	3 (2.7)	1 (4.5)	2 (2.3)	0.49
Salmonella sp.	1 (0.9)	0	1 (1.1)	1.00
Polymicrobial bacteremia[a]	13 (11.8)	3 (13.6)	10 (11.4)	0.72
Severe sepsis or septic shock	38 (34.5)	15 (68.2)	23 (26.1)	<0.001
Empirical antibiotic therapy				
Use of carbapenem	18 (16.4)	5 (22.7)	13 (14.8)	0.35
Inappropriate antibiotics	57 (51.8)	10 (45.5)	47 (53.4)	0.50
Definitive antibiotic therapy[b]				
Use of carbapenem	85 (78.7)	13 (65.0)	72 (81.8)	0.13
Inappropriate antibiotics	9 (8.3)	5 (25.0)	4 (4.5)	0.01

[a] 2 or more organisms (including non-ESBL/AmpC producers) isolated in blood culture samples taken within the first 24 h.
[b] 2 patients died before blood culture results were available, hence were excluded from analysis of definitive antibiotic therapy.

Table 4 Sub-analysis of association between empirical antibiotic therapy and mortality among patients with severe sepsis or septic shock.

Variables	All patients n = 38 (%)	Death n = 15 (39.5%)	Survival N = 23 (60.5%)	p value
Empirical antibiotic therapy				
Use of carbapenem	7 (18.4)	4 (26.7)	3 (13.0)	0.40
Inappropriate antibiotics	18 (47.4)	7 (46.7)	11 (47.8)	0.94

Table 5 Multivariate analysis of predictors for 30-day mortality.

Predictors	Death RF+	Death RF−	Crude OR (95% CI)	Adjusted OR (95% CI)
Hematological malignancy	11/33 (33.3%)	11/77 (14.3%)	3.00 (1.14−7.88) p = 0.03	
Immunosuppressive treatment	14/49 (28.6%)	8/61 (13.1%)	2.65 (1.01−6.98) p = 0.05	
Neutropenia	10/24 (41.7%)	12/86 (14.0%)	4.41 (1.60−12.16) p < 0.01	
Hospital acquired infection	12/40 (30%)	10/70 (14.3%)	2.57 (0.99−6.66) p = 0.05	
Urinary tract source	3/44 (6.8%)	19/66 (28.8%)	0.18 (0.05−0.66) p < 0.01	
Respiratory source	4/7 (57.1%)	18/103 (17.5%)	6.30 (1.30−30.60) p = 0.02	11.77 (1.30−106.85) p = 0.03[a]
Unknown source	9/26 (34.6%)	13/84 (15.5%)	2.89 (1.06−7.87) p = 0.04	
Severe sepsis or shock	15/38 (39.5%)	7/72 (9.7%)	6.06 (2.19−16.72) p = 0.001	5.17 (1.37−19.55) p = 0.02[a]
Inappropriate definitive antibiotics	5/9 (55.6%)	15/99 (15.2%)	7.00 (1.68−29.10) p < 0.01	27.93 (3.69−211.35) p = 0.001[a]

RF+, positive risk factor.
RF−, negative risk factor.
[a] Statistical significance with $p < 0.05$.

ESBL-E or AmpC-E BSI may be associated with higher rate of treatment failure and mortality due to lack of effective antibiotic therapy. Chavada et al., in a recent study of 114 patients with ESBL-E bacteremia in South Western Sydney revealed a crude mortality rate of 18.4% [38]. Our study corroborates the relatively high mortality rate of 20% in patients with ESBL-E and AmpC-E bacteremia. While inappropriate empirical antimicrobial therapy is often presumed to be the main contributing factor of mortality in ESBL-E or AmpC-E related sepsis, we did not find this association in our analysis. In a study of 232 patients with ESBL-E bacteremia in Dutch hospitals, Florine et al. found that inadequate therapy within first 24 h did not increase day 30 mortality [26]. Similarly, Chavada et al. concluded that inappropriate definitive therapy, rather than initial empirical therapy was associated with increased mortality [38].

We believe our patients succumbed primarily due to their underlying diseases and severity of sepsis at presentation. Higher mortality was found in patients who were neutropenic or immunosuppressed due to underlying haematological malignancy or immunosuppressants use. Similar observations were noted in studies by Menashe et al. [39] and Park et al. [40]. Immunocompromised hosts are known to be susceptible to severe infection and rapid progression of sepsis. In our cohort, severe sepsis and pneumonia appeared to be independent predictors of death. Prompt resuscitation, early admission to intensive care unit and adequate source control are perhaps more crucial to the survival of patients with ESBL-E and AmpC-E bacteremia than initial antibiotic choices.

Furthermore, we did not find any difference in outcomes between patients treated empirically with carbapenem and non-carbapenem antibiotics. It is a common notion among clinicians that carbapenem should be empirically initiated for any patients suspected of ESBL or AmpC related infections. Such practice may contribute to carbapenem overuse in hospitals with high prevalence of ESBL and AmpC isolates and may not improve the overall survival rate as demonstrated in our study.

The time has come to balance the recommendation for early carbapenem for all patients with possible ESBL or AmpC sepsis and the possible harm associated with unnecessary broad-spectrum antibiotics. In this era of drying antibiotic pipeline, carbapenems should be reserved for critically ill and hemodynamically unstable patient [41]. For stable patients, some non-beta-lactam empirical antibiotics recommended by our local antibiotic guidelines should provide adequate cover for ESBL or AmpC infection. For instance, the Australian Therapeutic Guideline suggests adding intravenous gentamicin empirically for patients with severe urinary tract infection, intraabdominal sepsis or suspected sepsis of unknown cause [42]. With 78.2% gentamicin susceptibility among our ESBL and AmpC isolates, combining gentamicin with first line agents such as ampicillin or ceftriaxone appears to be reasonable in the context of suspected ESBL or AmpC sepsis.

Piperacillin−tazobactam, which was commonly prescribed for nosocomial infections and immunocompromised hosts, had slightly higher resistance rate (40%) among our isolates. A study in Singapore demonstrated that empiric piperacillin−tazobactam was not associated with increased 30-day mortality and may result in fewer multi-drug resistant and fungal infections when compared with a carbapenem [12]. Conversely, in a John Hopkins Hospital cohort of 331 ESBL bacteraemia episodes, the adjusted risk of death was 1.92 times higher for patients receiving empiric piperacillin−tazobactam compared with empiric

carbapenem therapy (95% confidence interval, 1.07—3.45). The authors suggested that for patients at high risk of invasive ESBL infections, early carbapenem therapy should be considered [43].

As inappropriate definitive therapy was independently associated with 30-day mortality, emphasis should be on early detection of ESBL and AmpC isolates. At the Alfred Hospital, our microbiology registrar or laboratory scientists would routinely communicate with treating doctors whenever ESBL or AmpC-producing bacteria were identified. With the availability of automated Vitek 2 system in our laboratory, which could provide an identification and preliminary antibiotic susceptibility of the bacteria as soon as 24 h, our clinicians were able to make early appropriate switch to definitive therapy if necessary.

This study has several limitations. Our single-center study results may not be generalizable to patients in other hospitals. Due to the retrospective nature of our study, we could not control for potential confounding factors, such as the timing of switching from empirical to definitive therapy and total duration of antibiotics. Furthermore, few of our patients had been commenced on palliative care pathway which might influence the antimicrobial decision and outcome. As our study was dependent on inpatient records, we could only analyse objective and easily measurable outcomes like all-cause mortality in hospital. In addition, this was not a case-control study, therefore we were unable to generate reliable risk factors of ESBL-E and AmpC infections. As the prevalence of ESBL-E and AmpC-E is still low in Australia, prediction rules might be helpful in identifying patients who should be receiving empirical treatment for these organisms.

Although the choice and appropriateness of empirical therapy were not associated with day 30 mortality in ESBL-E and AmpC-E bacteremia, adequacy of initial treatment may be improved by review of patient's risk factors such as hematological malignancy, immunosuppressive therapy, antibiotic history and ESBL/AmpC colonization. Empirical carbapenem should be reserved for those who presented with severe sepsis or pneumonia, both of which were independent risk factors for 30-day inpatient mortality. Otherwise, empirical antibiotic prescription should be in line with local antibiotic guidelines, with gentamicin being a reasonable option for suspected ESBL-E and AmpC-E sepsis. Emphasis should be placed on prompt resuscitation of patient in severe sepsis, early detection of ESBL-E and AmpC-E isolates and appropriate switch to definitive therapy to ensure favourable outcome.

Ethics

The study was approved by Alfred Hospital Ethics Committee.

Authorship statement

CL Lim conducted the data collection, analysed the data, drafted, revised and finalized the paper for submission. D Spelman conceived the idea, reviewed the draft, and made edits and comments.

Conflict of interest

The authors declare that there is no conflict of interest.

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